MODELING THE EVAPORATIVE LOSS OF ORGANOPHOSPHORUS PESTICIDES FROM SKIN USING THE EXPOSURE RELATED DOSE ESTIMATING MODEL (ERDEM)

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Introduction

Evaporation of pesticides off foliage (Gunther et al., 1973), household surfaces, and skin surfaces were reported by Reifenrath and Robinson, 1982, Hawkins and Reifenrath, 1984; Reifenrath and Spencer, 1989; Wester et al., 1992, Knaak et al., 1984, 1990 and 2002 and Zendzian, 2000.

Controlled in vitro pig-skin penetration and evaporation studies conducted by Hawkins and Reifenrath (1984) indicated that air flow, temperature and humidity directly affected evaporation and penetration, with an increase in temperature (24 to 32°C) and humidity resulting in less evaporation and more penetration. Hawkins and Reifenrath reported that losses to air occurred during penetration.

Wester et al. (1992) reported on the evaporative loss of topically applied isofenphos from skin of human volunteers. Small quantities of isofenphos (13.2 μg/cm²) readily evaporated, the surface dose being minimal at 24 h, with approximately 40% being lost 15 minutes post application. Rapid loss was not observed in rat studies (Knaak et al., 1990) involving isofenphos, but it was observed in studies with parathion (Knaak et al., 1984). Initial losses amounting to 25% of the applied dose were associated with topical applications of parathion. Zendzian (2000) reported the loss of 23 to 36% of disulfoton and 16 to 26% of mevinphos from rat skin, 10 h after topical application. Table 1 relates vapor pressure and evaporative loss for a number of topically applied pesticides/compounds. Although the relationship is not perfect, the Table strongly supports evaporation as a pathway involved in the removal of pesticide residues and supports the results of the studies reported by Zendzian (2000) on volatile pesticides.

The relationship between the fate (i.e., amounts evaporated, wash-off and absorbed) of topically applied parathion and isofenphos to human skin and the method of application (i.e., single bolus applications and transferred leaf residues) was examined using the Exposure Related Dose Estimating Model (ERDEM).

Methods

ERDEM was developed at EPA, Las Vegas and used to describe the multiroute absorption of parathion, isofenphos and chlorpyrifos in children (Knaak et al., 2000). The model was based upon percutaneous absorption studies in the rat involving unoccluded single topical applications (Knaak et al., 1984, 1990) and the PBPK/PD models of Knaak et al., 2002.

ERDEM was upgraded by adding or modifying equations to depict pesticide transfer to skin ($k_d R$) and their disappearance from the surface of the skin due to evaporative loss ($K_a A_{surf}$), penetration ($K_p a(C_{surf} - C_{sk})$) and wash-offs ($K_a A_{surf}$):

$$dA_{surf}/dt = K_p a (C_{sk} - C_{surf}) - K_a A_{surf} + k_d R$$

The model keeps track of skin surface residues during single and repeated periods of daily exposure, pesticide residues washed-off at the end of the workday, and the absorbed dose (i.e., amounts and concentrations in tissues, and amounts eliminated in urine and feces). Factors such as concentration (C, μg/cm³) of the topical dose, exposed skin area (a), permeation constant (K_p), evaporation and wash-offs (K_a) and transfer coefficients ($k_d R$) may be readily changed in the model.

The fate of parathion and isofenphos were modeled according to the following scenarios:
1) Single topical applications followed by 8 h of exposure, wash-off and 24 h of metabolism (topical dose equivalent to a spray or other residue left on for 8 h.)
2) Single topical applications followed by 168 h of exposure (topical dose equivalent to a spray or other residue left on for 168 h).
3) 5 day repeated topical applications with daily wash-off after 8 h of exposure and 5 days of metabolism (topical dose equivalent to receiving a spray or other residue every day for 5 days with wash-off at the end of the work day)
4) Transfer and loss of parathion from the skin of field workers reentering pesticide-treated foliage during a 5 day workweek, daily wash-off after 8 h of exposure, 5 days of metabolism.
5) Transfer and loss of isofenphos from the skin of individuals coming in contact with treated turf during 5 days of exposure, wash-off after 8 h of exposure and 5 days of metabolism.

Results and Discussion

The results in Tables 2 and 3 for parathion and isofenphos indicate that topical applications (i.e., spray residues) of these two OP pesticides are largely retained on skin after 8 h of exposure (76.5 to 89.7%), lost by volatilization (5 to 19%) or absorbed (4.5 to 5.3%). Similar results were obtained with 5 day repeated applications after 8 h of exposure (wash-off). Model outputs (ERDEM) are shown in Figure 1 (A, B, C) for parathion. Five daily 8 h exposures followed by wash-off (Fig 1A) resulted in cumulative levels of pesticide going to air (Fig 1B) and being eliminated in urine and feces over 5 days (Fig 1C). The initial sharp rise in the amount of parathion going to air (Fig 1B) was caused by rapid volatilization shortly after application. This did not occur with isofenphos in rat studies. However, the results of human studies performed by Wester et al. (1992) at the bottom of Fig 3 indicate that isofenphos is rapidly lost during or shortly after application. This may occur when isofenphos is deposited on skin from a spray. The probably that isofenphos evaporates from dust is believed to be low.

Five day repeated exposure to pesticides residues (transferred from citrus leaves and turf, 8 h daily exposure) resulted in less absorption (2.7%) and volatilization (2.1 to 2.6%) with more pesticide being retained on skin prior to wash-off. The plots from the parathion model (ERDEM) are shown in Figure 2 (A, B, C). In Fig 2A, the transfer coefficient produced a slow rise in the amount(s) on skin, while wash-off after 8 h rapidly removed pesticide residues. When parathion and isofenphos (spray or other residues) were left on rat skin (in vivo) for a period of 168 h, 44 to 48% of the applied dose was lost to air, 41.6 to 46% was absorbed with 10% of the applied dose being retained on skin.

The results show that evaporation may play an important role in removing pesticide residues from skin, however, the persistence of pesticide residues on the surface of the skin support pesticide regulations requiring showering and wearing clean clothing. The importance of evaporation in reducing pesticide residues on skin deposited under field conditions needs to be further investigated. The model assumed all parathion and isofenphos residues were biologically available for dermal absorption, were washed off at the end of the workday (8 h) and little or no residues penetrated skin during showering.

We believe PBPK/PD models such as ERDEM should be used in conjunction with field or controlled studies to assist in determining whether or not evaporation plays an important role in removing pesticide residues from skin under field conditions as suggested by controlled rat or human studies.
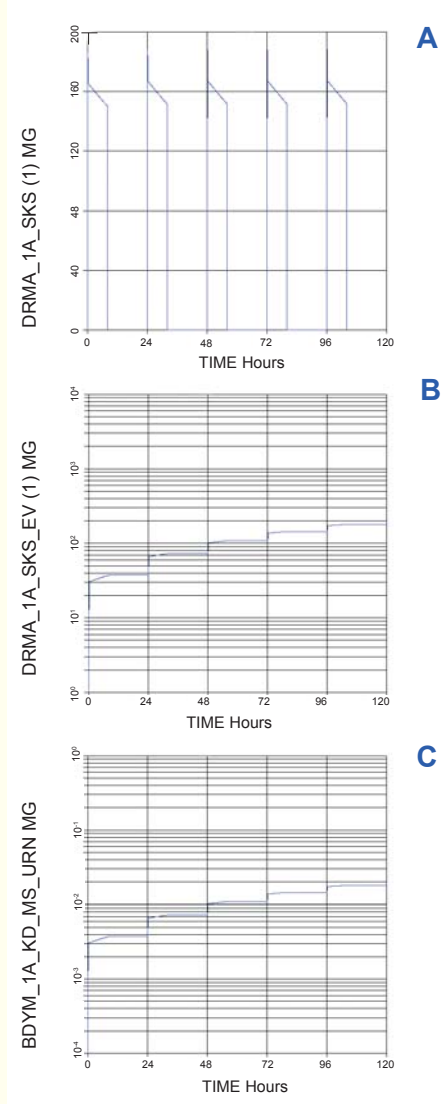

Figure 1. Fate of topical applications of parathion to humans (5 day repeat applications, daily wash-off after 8 h of exposure).

A. Residues on skin
B. Lost to air and
C. Cumulative excretion in urine and feces.

Figure 2. Fate of parathion citrus residues transferred from leaf surfaces to skin (5 day repeat exposure, daily wash-off after 8 h of exposure).

A. Residues on skin
B. Lost to air and
C. Cumulative excretion in urine and feces.

Table 1. Comparison of Vapor Pressure and Evaporation Loss of Topical Application of Radiolabeled Compounds to Skin.

Compound	Vapor Pressure (mm Hg at 20°C)	Evaporation Loss; Percent of Applied Radioactive Dose
DDT	1.5×10^{-7}	4 +/- 5[a]
Isofenphos	1.65×10^{-6}	44[c] in vivo human (model)
Isofenphos	1.65×10^{-6}	96 +/- 2[b] in vivo human skin (volunteers)
Parathion	4.7×10^{-6}	7 +/- 0.6[a]
Parathion	4.7×10^{-6}	38.6[d] in vivo human (model)
Malathion	5.5×10^{-6}	17 +/- 8[a]
Chlorpyrifos	1.8×10^{-5}	46e[e] in vivo human skin (volunteers)
Chlorpyrifos	1.8×10^{-5}	(model)
Lindane	3.3×10^{-5}	26 +/- 5[a]
Benzoic acid	3.8×10^{-4}	5.7 +/- 0.3[a]
N,N-Diethyl-m-toluamide	1.03×10^{-3}	21 +/- 6[a]
Diethyl malonate	2.49×10^{-1}	40 +/- 10[a]
Diisopropyl fluorophosphonate	5.79×10^{-1}	65 +/- 8[a]

Source: [a] Hawkins and Reifenrath (1984), in vitro study using fresh pig skin, Tyrodes solution perfusing the penetration cell at 5 ml/h, air at 24°C flowing through the evaporation manifold at 60 ml/min and compounds applied at 4 μg/cm². Collections terminated at 50 h.

[b] Wester et al., (1992). Isofenphos applied to 12 cm² of volunteer skin at 13.2 μg/cm², 24 h exposure.

[c] Table 3, model, isofenphos applied to 1000 cm² of human skin at 224 μg/cm², 168 h exposure period. Evaporation rate constant from rat PBPK/PD model, Knaak et al., 2002.

[d] Table 2, model, parathion applied to 1000 cm² of human skin at 196 μg/cm², 168 h exposure period. Evaporation rate constant from rat PBPK/PD model, Knaak et al., 2002.

[e] Griffin et al. (1999) applied chlorpyrifos (31.5 μg/cm²) to 78 cm² of skin (human volunteers) for an exposure period of 100 h. Approximately 53% recovered in skin washings, 1% in urine, and 46% of the dose unaccounted for (evaporation).

Table 2. Fate of Parathion Topically Administered or Transferred to Human Skin from Treated Leaves in Percent of Dose (Output from ERDEM).

	Single topical dose, daily wash-off after 8 h exposure, 24 h of metabolism $K_a = 0.8$ h-1 for 0.25 h, 0.0055 hr-1 for 7.75 h	Single topical dose, 168 h exposure, 7 day metabolism $K_a = 0.0055$ h-1 for 168 h	5 day repeated topical doses, daily wash-off after 8 h of exposure, 5 day metabolism $K_a = 0.8$ h-1 for 0.25 hr, 0.0055 hr-1 for 7.75 h	5 day repeated skin exposure (transfer coefficient), wash-off after 8 h of exposure, 5 day metabolism $K_a = 0.0055$ h-1 for 8.0 h
Applied Dose/absorbed dose (mg)	195.9/8.8 4.5% absorbed 0.13 mg/kg	195.9/81.5 41.6% absorbed 1.2 mg/kg	980/44.5 4.5% absorbed 0.64 mg/kg	400/10.9 2.7% absorbed 0.16 mg/kg
Parathion (% of dose)				
Loss to air	19.0	48.1	18.3	2.1
Retained on skin/or wash-off	0.0/76.5	10.4/0.0	0.0/77.1	0.0/95.2
Urine and Feces	1.9	28.9	2.7	1.6
Tissues	2.6 (5.09 mg)	12.7 (24.9 mg)	1.9 (18.6 mg)	1.1 (4.4 mg)
Total	100.0	100.0	100.0	100.0
Parathion and metabolites in compartments (% of tissue residues)				
Parathion (in fat, etc.)	40.6 (2.1 mg) 0.03 mg/kg	23.9 (6.0 mg) 0.09 mg/kg	31.1 (5.8 mg) 0.08 mg/kg	31.1 (1.4 mg) 0.02 mg/kg
Alkyl phosphates (fat)	2.6	0.96	1.50	1.5
p-nitrophenol (p-NP)(fat)	1.4	0.29	0.48	0.50
Sulfate of p-NP (SP)	0.34	0.086	0.12	0.13
Glucuronide of p-NP (SP)	0.34	0.066	0.12	0.12
Inhibited (liver) enzymes	10.2	11.8	11.5	12.2

Parathion dermal human dose = 2.8 mg/kg (6.729 x 10⁸ pmol); BW = 70 kg, area = 1000 cm², $K_p = 0.007$ cm/h, $K_a = 0.0055$ h⁻¹

Parathion transfer coefficient, $K_d = 10,000$; surface residues, R = 1.0 μg/cm²

Table 3. Fate of Isofenphos Topically Administered or Transferred to Human Skin from Treated Leaves in Percent of Dose (Output from ERDEM).

	Single topical dose, daily wash-off after 8 h exposure, 24 h of metabolism $K_a = 0.006$ $K_a = 0.0067$ h⁻¹ for 8.0 h	Single topical dose, 168 h exposure, 7 day metabolism $K_a = 0.0067$ h⁻¹ for 168 h	5 day repeated topical doses, daily wash-off after 8 h of exposure, 5 day metabolism $K_a = 0.006$ $K_a = 0.0067$ h⁻¹ for 8.0 hr	5 day repeated skin exposure (transfer coefficient), wash-off after 8 h of exposure, 5 day metabolism $K_a = 0.0067$ h⁻¹ for 8.0 h
Applied Dose/absorbed dose (mg)	224/11.8 5.3% absorbed 0.17 mg/kg	224/103.0 46.0% absorbed 1.5 mg/kg	1119.9/59.2 5.3% absorbed 0.85 mg/kg	400/10.9 2.7% absorbed 0.16 mg/kg
Isofenphos (% of dose)				
Loss to air	5.05	44.0	5.05	2.6
Retained on skin/or wash-off	0.0/89.7	10.2/0.0	0.0/89.7	0.0/94.7
Urine and Feces	2.6	37.1	3.8	1.9
Tissues	2.7 (6.05 mg)	8.9 (19.9 mg)	1.5 (16.7 mg)	0.8 (3.2 mg)
Total	100.0	100.0	100.0	100.0
Isofenphos and metabolites in compartments (% of tissue residues)				
Isofenphos (in fat, etc.)	32.1 (1.9 mg) 0.03 mg/kg	15.2 (3.02 mg) 0.04 mg/kg	22.1 (3.7 mg) 0.05 mg/kg	22.3 (0.71 mg) 0.01 mg/kg
IFA (fat)	2.9	0.50	0.98	1.03
Alkyl phosphates (fat)	0.22	0.04	0.07	1.07
IPS (fat)	0.80	0.12	0.26	0.28
SA (fat)	0.58	0.10	0.21	0.22
2OH-HA (SP)	0.46	0.08	0.16	0.17
Inhibited (liver) enzymes	0.03	0.04	0.03	0.03

Isofenphos dermal human dose = 3.2 mg/kg (6.485 x 10⁸ pmol); BW = 70 kg, area = 1000 cm², $K_p = 0.007$, $K_a = 0.0067$

Isofenphos transfer coefficient from turf: $K_d = 10,000$; surface residues, R = 1.0 mg/cm²

IPS = isopropyl salicylate, SA = salicylic acid, 2OH-HA = glycine conjugate of SA

Recovery of isofenphos from the skin of human volunteers (Wester et al., 1992)

0 h, 61.4%, 1 h, 54.1%, 2 h, 54.9%, 4 h, 43.5%, 8 h, 30.3%, 24 h, 0.53% (3% in urine)

Conclusions

1) Volatility (evaporation) plays an important role in removing parathion and isofenphos from skin of animals and humans under controlled conditions involving a single bolus dose (i.e, deposited from spray or other source).

2) ERDEM indicated that evaporation is not very important in removing parathion and isofenphos residues transferred to skin during reentry based on using evaporation rates determined with rats under laboratory conditions.

3) ERDEM indicated that parathion and isofenphos residues transferred to skin during reentry largely reside on the surface of the skin and must be removed by showering at the end of the workday.

4) ERDEM assumed 100% of the residue on the surface of the skin is washed off during showering resulting in little or no penetration. Information regarding the efficacy of showering needs to be incorporated in the model.

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